Appl. No. : **09/315,292**
Filed : **May 20, 1999**

REMARKS

Claims 99-121 were pending.

Applicants have amended claim 99 to replace "a plurality" with "at least one." Support for this amendment can be found throughout the specification as filed, for example, at page 3, lines 20-25.

Applicants have added new claims 122-127. Support for new claims 122-125 can be found throughout the specification as filed, for example, at page 69-70, Tables 2-3. Support for new claims 126-127 can be found throughout the specification as filed, for example, at page 67.

Applicants have canceled claims 108, 118 and 120 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Accordingly, claims 99-107, 109-117, 119, 121-127 are pending and under consideration.

35 U.S.C. § 112, First Paragraph – New Matter

The Examiner rejects claims 99-119 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that a "plurality" and "at least about half" as recited in claims 99, 108 and 118 lack support in the specification, and therefore constitute new matter. The Examiner invites the applicants to point out with particularity where support for the claim amendments "filed on 2/15/08" can be found.

Applicants note that the objected to claim amendments a "plurality" and "at least about half," were filed on August 1, 2008, not February 15, 2008. As stated in the response filed on February 15, 2008, support for the amendments filed in that response can be found, for example, at original claims 37-51; page 16, lines 25-28; page 23, lines 7-10 and 30-34; page 34, lines 9-31; and Examples 2 and 3, beginning on page 61.

With respect to the objected amendments filed on August 1, 2008, reciting "a plurality" and "at least about half," without acquiescing to the Examiner's rejection, and solely in the interest of advancing prosecution, Applicants have amended claim 99 to replace "a plurality" with "at least one," and have canceled claims 108 and 118. Applicants therefore request that the Examiner withdraw the rejection of the pending claims as lacking written description support.

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The Examiner alleges that support for the pending claims cannot be found in the priority document. Applicants respectfully disagree. The claimed method and oligonucleotide can be found at Examples 2-3, specifically see summary Tables 2-3, of priority document USSN 09/083,586. Accordingly, the claimed invention benefits from the priority date of 5/21/98 for USSN 09/083,586.

35 U.S.C. § 103(a) – Obviousness

Claims 99-121 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, (WO 96/40266) in view of Nicklin *et al.* (WO 98/09633) and Levesque *et al.*, (Mol. Pharmacol., 51, 1997, 209-216). *Office Action* at 5. The Examiner asserts that Nyce discloses the invention with the exception of 2'-O-methoxyethyl and 5-methylcytosine modifications. *See Office Action* at 6. The Examiner asserts that Nicklin and Levesque disclose the missing elements, that it would have been obvious to modify the antisense of Nyce to include the modifications of Nicklin and Levesque, and that the level/degree of modification amounts to routine optimization. Applicants respectfully traverse.

Applicants submit that it is improper to use hindsight to restrict the number of possible variables that would have to be modified/optimized to arrive at the claimed invention. *See M.P.E.P. §2142* (The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.)

Starting with the disclosure of Nyce, a reason must be articulated why one of skill in the art would modify the oligonucleotide of Nyce to arrive at the claimed invention. The Examiner states that "[o]ne would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications into the oligonucleotides of the method of Nyce et al. because Nicklin teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target." *Office Action* at 7.

Nicklin discloses literally hundreds of preferred modifications which one of skill in the art would have to try if one were to modify the oligonucleotide of Nyce based on Nicklin. *See Nicklin* at 2-5. Since *KSR*, the Federal Circuit has reiterated that "obvious to try" is not the same

as obvious under §103. For example, the court has affirmed its earlier holding in *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), that obviousness cannot be based on facts where what is obvious to try is "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave ... no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d at 903 (emphasis added).

Given the number of modifications disclosed in Nicklin, and the fact that Nicklin discloses that one of the "especially preferred embodiments" is one which contains no 2'-modified nucleotides (*Nicklin* at 4), Appellants submit that the instant case one in which what is obvious to try is "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave ... no direction as to which of many possible choices is likely to be successful." *O'Farrell*, 853 F.2d at 903 (emphasis added). As such, "obvious to try" in the instant case cannot be equated with obviousness under 35 U.S.C. § 103(a).

In addition, even if a *prima facie* case of obviousness has been established, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected results. "The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that 'evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.'" *M.P.E.P. §716.01(a)* (emphasis added).

Applicants have found that incorporating 2'-O-methoxyethyl nucleosides improves the uptake of oligonucleotides into cells of the lungs. Example 3 of the instant application discloses the results of *in vivo* administration of aerosolized nucleotides into the lung. Tables 2 and 3 show the concentration of oligonucleotide in the lungs of mice following single and multiple administrations, respectively, of three antisense molecules. Importantly, ISIS 15163 performs more than 3 times better than ISIS 17009, even though the only difference between the two molecules is the fact that ISIS 17009 does not contain any 2'-O-methoxyethyl nucleosides, while ISIS 15163 does. That 2'-O-methoxyethyl improves pulmonary uptake is clearly unexpected in view of the cited references, which do not teach that 2'-O-methoxyethyl modifications improve cellular uptake.

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The fact that this result is unexpected is supported by the declaration of Dr. Richard Geary, attached as Exhibit 1. Dr. Geary, an expert in the field of antisense technology, with over 14 years experience in the field, states that:

> [A]t the time of the invention, one in the field would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung. At the time of the invention, the inclusion of one or more, a majority, or even full 2'-O-methoxyethyl modifications in a nucleic acid was thought to potentially increase stability of the nucleic acid and/or increase affinity of the nucleic acid to a complementary strand. In my experience, the distribution of oligonucleotide following parenteral dosing of oligonucleotides containing 2'-O-methoxyethyl modifications was essentially identical to the first generation modified oligonucleotides containing only phosphorothioate backbone modifications. As a result, I and my colleagues concluded that the phosphorothioate backbone guided distribution and uptake, not 2'-O-methoxyethyl modification.
>
> The fact that the inclusion of 2'-O-methoxyethyl modifications improved cellular uptake into cells of the lung is demonstrated by the results of Table 2 and 3 of the above-captioned application. ISIS 17009 and ISIS 15163 differ only in the inclusion of 2'-O-methoxyethyl modifications in ISIS 15163, yet ISIS 15163 shows more than three times the concentration in lung cells as compared to ISIS 17009 at the highest administered dose. This effect is seen for both single administration (Table 2) and multiple administration (Table 3) experiments. It is my expert opinion that at the time of the invention, this result was unexpected. *Geary Declaration* at ¶¶5-6 (emphasis added).

The Examiner responds to Applicants' assertion that the results in Tables 2 and 3 showing vastly improved uptake into lung cells are unexpected by asserting that "[i]ncorporation of a plurality of 2'-O-methoxyethyl modifications as well as each of the other structural elements of the instant claims in any configuration within the oligonucleotide is considered within the realm of routine optimization of the oligonucleotide of Nyce and is certainly not an unexpected result in view of the scope of the instant claims." *Office Action* at 12.

Applicants respectfully submit that even *if* the cited references suggest the addition of 2'-O-methoxyethyl modifications to the oligonucleotides of Nyce, the references do not suggest that this modification would in any way improve the uptake of the oligonucleotide into cells of the lung. At best, Nicklin confirms, as was understood by one of skill in the art at the time, that modification of nucleotides at the 2' position of the sugar "increase target binding affinity." *Nicklin* at 3. Applicants' are not aware of any statements in the cited references which suggest

that 2'-sugar modifications in general, or 2'-O-methoxyethyl modifications in particular, improve cellular uptake in the cells of the lung by any route of administration, let alone by aerosolized administration into the lungs in particular. And, according to an expert in the field, at the time of the invention one of skill in the art would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung. *Geary Declaration* at ¶5.

For at least the above reasons, Applicants submit that the pending claims are patentable over Nyce, in view of Nicklin, and Levesque. Applicants therefore request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

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CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 5/6/09

By: _____

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Exhibit 1

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Bennett, et al.
Appl. No.	:	09/315,292
Filed	:	May 20, 1999
For	:	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS
Examiner	:	Bowman, Amy Hudson
Group Art Unit	:	1635

DECLARATION OF RICHARD GEARY, Ph.D., UNDER 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Dr. Richard Geary, declare and state as follows:

1. I am a scientist at Isis Pharmaceuticals, Inc., which is the assignee of the above-captioned application. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

2. I am an expert in the field of the invention, with over 14 years of experience in the design and testing of nucleic acid molecules as therapeutics. I have extensive knowledge regarding the subject matter of the above-captioned application, including sugar modifications of nucleic acids.

3. I am informed that the Examiner has asserted that at the time of the above captioned invention, a person of ordinary skill in the art would have been motivated to incorporate 2'-O-methoxyethyl and 5-methylcytosine modifications into the oligonucleotides of Nyce et al. (WO 96/40266) because Nicklin et al. (WO 96/09633) teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target.

4. I have reviewed Nicklin et al. and do not find support for the assertion that incorporation of 2'-O-methoxyethyl modifications would result in increased uptake of a nucleic acid into cells. The specific section of Nicklin asserted to teach that modifications of antisense oligonucleotides confer increased uptake into cells does not suggest that 2' modifications are capable of increasing cellular uptake. Rather, Nicklin et al. confirm, as was understood at the time, that modification of the 2' position of the nucleotide sugar increases target binding affinity. *Nicklin* at pages 2-3.

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5. It is my expert opinion that at the time of the invention, one in the field would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung. At the time of the invention, the inclusion of one or more, a majority, or even full 2'-O-methoxyethyl modifications in a nucleic acid was thought to potentially increase stability of the nucleic acid and/or increase affinity of the nucleic acid to a complementary strand. In my experience, the distribution of oligonucleotide following parenteral dosing of oligonucleotides containing 2'-O-methoxyethyl modifications was essentially identical to the first generation modified oligonucleotides containing only phosphorothioate backbone modifications. As a result, I and my colleagues concluded that the phosphorothioate backbone guided distribution and uptake, not 2'-O-methoxyethyl modification.

6. The fact that the inclusion of 2'-O-methoxyethyl modifications improved cellular uptake into cells of the lung is demonstrated by the results of Table 2 and 3 of the above-captioned application. ISIS 17009 and ISIS 15163 differ only in the inclusion of 2'-O-methoxyethyl modifications in ISIS 15163, yet ISIS 15163 shows more than three times the concentration in lung cells as compared to ISIS 17009 at the highest administered dose. This effect is seen for both single administration (Table 2) and multiple administration (Table 3) experiments. It is my expert opinion that at the time of the invention, this result was unexpected.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: _____ Date: 5/6/09
Richard Geary, Ph.D.

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